IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 5256
WILLIAMS *et al.*	Art Unit: 1652
Appl. No. 09/839,946	Examiner: Saidha, T.
Filing Date: April 19, 2001	Atty. Docket: 2057.0090003/BJD/SAC
For: **PEG-Urate Oxidase Conjugates and Use Thereof**	

Reply Brief Under 37 C.F.R. § 41.41

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Commissioner for Patents
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Sir:

Appellants filed a Brief on Appeal to the Board of Patent Appeals and Interferences for the above-captioned application on April 20, 2006. The appeal is directed to the final rejection of claims 50-53 under 35 U.S.C. §§ 102 as set forth in the Office Action dated July 20, 2005 and the Advisory Action dated December 5, 2005. The Examiner's Answer was mailed July 11, 2006, and reiterated many of the erroneous contentions and conclusions that have been advanced by the Examiner in the Office Actions issued in this application, as well as offering several new errors in fact and law. Therefore, in reply to the Examiner's Answer, Appellants submit this Reply Brief Under 37 C.F.R. § 41.41.

I. Claims 50-53 Are Not Anticipated By Lee

Claims 50-53 were rejected under 35 U.S.C. § 102(b) as anticipated by Lee *et al.*, *Science 239*:1288-1291 (1988) (hereinafter "Lee"). In the Examiner's Answer, the Examiner continues to rely on Lee as allegedly teaching an isolated tetrameric

mammalian uricase, wherein at least about 90% of said uricase is in a tetrameric form and less than about 10% of said uricase is in a non-tetrameric aggregated form. However, Appellants respectfully reassert that Lee does not teach every element recited in claims 50-53. Therefore, the Examiner's continued rejection of claims 50-53 based on 35 U.S.C. § 102(b) over Lee is legally and factually unfounded.

To establish a *prima facie* case of anticipation under § 102(b), the Examiner must show that "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). *See also Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert denied*, 465 U.S. 1026 (1984). Because the Examiner has failed to establish that each and every element of claims 50-53 is described, either expressly or inherently, in Lee, this rejection of claims 50-53 must be reversed.

A. The Examiner's Analysis of the Disclosure of Lee is Erroneous

In the Examiner's Answer, the Examiner asserts that Lee teaches "the recombinant production of full length amino acid sequence of porcine Urate oxidase (also known as uricase) (see abstract lines 8-10) which is tetrameric and is substantially pure." *See* Examiner Answer at page 5. Appellants respectfully disagree with the Examiner's analysis of the teachings allegedly disclosed by Lee. First, Lee contains no disclosure regarding the expression and "recombinant production" of porcine urate oxidase. Instead, Lee is focused solely on determining the N-terminal amino acid sequence of porcine urate oxidase in order to generate a cDNA probe -- there is absolutely no disclosure in Lee of the expression, production and purification of a

tetrameric uricase. In support of his assertion that Lee teaches "the recombinant production of full length amino acid sequence of porcine Urate oxidase ... which is tetrameric," the Examiner cites to the abstract at lines 8-10 of Lee. However, Appellants respectfully point out that lines 8-10 of the abstract of Lee refer to isolation of "a full-length porcine urate oxidase cDNA," not of a porcine urate oxidase polypeptide. Moreover, as discussed above, there is absolutely no disclosure in Lee of the expression of a porcine oxidase polypeptide -- full length or otherwise -- from this cDNA molecule or from any RNA molecule transcribed from, or reverse transcribed into, this cDNA molecule. Therefore, the Examiner's assertions that Lee discloses "the recombinant production of full length amino acid sequence of porcine Urate oxidase . . . which is tetrameric and is substantially pure" are erroneous, and cannot be the basis for any rejection of the present claims.

B. The Mammalian Uricase with a Tetrameric Structure Disclosed in Lee Is Not A Tetrameric Uricase As Required By the Present Claims

Throughout the Examiner's Answer, the Examiner continues to assert that two statements made in Lee that (1) mammalian uricase exists as a tetramer with a subunit size of 32,000 daltons and (2) the uricase is "purified to homogeneity," fully support his contention that Lee discloses "an isolated tetrameric mammalian uricase" which is 100% in the tetrameric form. The Examiner then contends that because the present claims recite "an isolated tetrameric mammalian uricase, wherein at least 90% of the uricase is in the tetrameric form," the claims "when given the broadest reasonable interpretation" would encompass the uricase allegedly disclosed in Lee, namely a uricase which is 100% in the tetrameric form. However, Appellants respectfully assert that the statements in

Lee indicated above do not support the Examiner's contention that Lee discloses "an isolated tetrameric mammalian uricase" which is 100% in the tetrameric form. Hence, the Examiner's contentions, and the conclusions that rely upon them, are based on a completely erroneous reading of the disclosure of Lee.

First, Appellants respectfully remind the Examiner that a mammalian uricase with a tetrameric structure is not the same as isolated uricase being in a non-aggregated, tetrameric form (as claimed in the present invention).[1] As is clearly indicated in the present specification and discussed in Appellants' Brief on Appeal, prior to the present invention, it was not possible to isolate tetrameric uricase wherein at least about 90% of the uricase was in a tetrameric, non-aggregated form. Prior to the present invention, isolated preparations of natural and recombinant uricase, including those disclosed in Lee, contained a *mixture* of forms of the enzyme, including a high content of non-tetrameric aggregates. *See* specification at page 16, lines 5-16. Indeed, as is clearly explained in the present specification, the preparations used in Lee would not contain uricase in which at least about 90% of the uricase was in a tetrameric form and less than about 10% of the uricase was in a non-tetrameric aggregated form. *See* specification at page 16, lines 5-8. In making his contentions, the Examiner thus is ignoring the clear guidance of the present specification on this issue, and is instead relying on a completely erroneous reading of the disclosure of Lee which has absolutely no support in Lee or any other art cited by the Examiner. Therefore, despite the Examiner's contention, a

[1] Additionally, in the Final Office Action, mailed July 20, 2005, on page 6, the Advisory Action, mailed December 5, 2005, on page 5 and the Examiner's Answer, mailed July 11, 2006, at page 12, the Examiner asserted that Conley *et al.*, *J. Biochem. 187*: 727-732 (1980) (Exhibit B) which discloses uricase from pig liver consisting of four apparently identical subunits "further clarifies that the uricase is tetrameric [four subunits]." However, Appellants again point out that uricase being in a non-aggregated, purely tetrameric form (as in the present invention) is not the same as uricase having a tetrameric structure (as in the Conley reference).

mammalian uricase with a tetrameric structure, as disclosed in Lee, is not the same as an isolated uricase in a non-aggregated, tetrameric form as required by the present claims.[2]

C. "Homogeneous" Preparations of Uricase Disclosed in Lee are not Preparations, Wherein at Least 90% of the Uricase is in a Tetrameric Form

Lee's statement that the uricase is "purified to homogeneity" also does not support the Examiner's contention that Lee discloses "an isolated tetrameric mammalian uricase" which is 100% in the tetrameric form. Appellants respectfully disagree with the Examiner's assertion that Lee allegedly teaches homogenous preparations of porcine or murine uricase that are present in the tetrameric form. *See* Examiner's Answer at pages 5-6.

First, as discussed in the Appellants' Brief on Appeal, Lee does not expressly disclose the purification of tetrameric mammalian uricase as recited in the present claims of the application. Lee does not indicate that at least 90% of the purified uricase was in the tetrameric form. Indeed, Lee does not even indicate what form the *purified* uricase was, let alone that at least 90% (or 100%) of it was in the tetrameric form.

Second, the Examiner continues to ignore the fact that the only criterion for homogeneity that is mentioned by Lee is the method of Conley and Priest, *Preparative Biochemistry 9*:197-203 (hereinafter "Conley"). In this method, Conley (and therefore Lee) use polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate (SDS-PAGE) to "purify to homogeneity" the porcine liver urate oxidase. Thus,

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[2] Therefore, for the reasons indicated above, it is also irrelevant that Appellants have indicated that mammalian uricase has a tetrameric structure, despite the Examiner's assertions to the contrary. *See* Examiner's Answer at page 9 and 16-17.

"purification to homogeneity" means only that the monomeric uricase subunits are free of non-uricase polypeptides or fragments of the monomer. Therefore, as pointed out by the Examiner on page 12 of the Examiner's answer, this method produces the same result (*i.e.*, only the monomeric subunit form is observed on the gel) no matter what the state of aggregation of the uricase polypeptides -- tetramers, octamers, or otherwise.

Furthermore, in response to Appellants' statement that uricase preparations such as those available from Sigma (including Sigma Cat. No. U 3250, the particular commercially available uricase used in the studies in Lee; *see* reference 8 of Lee) contain substantial quantities (*i.e.*, more than about 10%) of the non-tetrameric form of the enzyme, the Examiner contends that "even if the composition of the Sigma uricase is what the Appellants are claiming it [to] be, the Sigma uricase was used in the work of Lee for further purification." *See* Examiner's Answer at page 13. However, as indicated above, the only *purification* method allegedly used in Lee was SDS-PAGE. The uricase purification method of Conley (and therefore Lee) does not involve the use of any chromatographic or electrophoretic separations, nor does it involve any analytical method that could detect the state of association or aggregation of the uricase polypeptides, no matter how homogenous the uricase polypeptides are. Therefore, as indicated above and in Appellants' Brief on Appeal, both Lee and Conley are completely silent about uricase preparations that are in the tetrameric form. Furthermore, neither Conley nor Lee uses any "purification method" that would result in an isolated uricase, wherein at least 90% of the uricase was in a tetrameric form.

Finally, in the Examiner's Answer, the Examiner contends that the "isolated uricase preparation of Lee is not monomeric as per Lee, and as explained in the rejection

and as admitted by the Appellants in their own arguments." *See* Examiner's answer at page 16. Appellants disagree with this statement. First, Appellants respectfully assert that the Examiner is mischaracterizing our alleged "admission." As discussed above and in footnote 2, it is irrelevant that Appellants have indicated that mammalian uricase has a tetrameric structure because a mammalian uricase with a tetrameric structure, as disclosed in Lee, is not the same as an isolated uricase in a non-aggregated, tetrameric form as required by the present claims. Second, Appellants again reiterate that (1) there is a difference between a mammalian uricase with a tetrameric structure and an isolated uricase being in a non-aggregated, tetrameric form (as is presently claimed); (2) commercial preparations of uricase used in the studies in Lee would contain substantial quantities (*i.e.*, more than about 10%) of the non-tetrameric form of the enzyme; and (3) the further *purification* methods of Lee consist only of SDS-PAGE which, as the Examiner has admitted, would only produce the monomeric subunit form of the uricase, no matter in what form the uricase was originally present. Thus, Lee does not disclose an isolated tetrameric mammalian uricase, wherein at least about 90% of said uricase is in a tetrameric form and less than about 10% of said uricase is in a non-tetrameric aggregated form as is presently claimed.

Consistent with this misconception regarding the disclosure of Lee, the Examiner suggests that Appellants do not recognize the distinction between native gel electrophoresis and SDS-PAGE denaturing gel electrophoresis. Despite this disingenuous comment by the Examiner, Appellants do indeed understand the difference; in fact, this difference is the key to Appellants' point. If native gel electrophoresis had been used in the methods of Lee, it would have been clear that the preparations of Sigma

uricase used by Lee were not "at least 90% in the tetrameric form" as required by the present claims. This is because one could have observed the migration of the uricase in the various aggregate forms of the commercial Sigma uricase which would have been present in a native gel. However, as indicated above, the *homogenous* preparation of uricase disclosed in Lee is in the form of monomers, formed from aggregates of the isolated Sigma uricase by the SDS-PAGE process disclosed in Conley.[3]

Given the discussion above and in Appellants' Brief on Appeal, Lee clearly discloses only preparations of uricase in which more than about 10% of the uricase is either: (a) in a non-tetrameric aggregated form (*i.e.*, the commercial preparation); or (b) in a monomeric form after SDS-PAGE analysis. Lee, therefore, does *not* disclose preparations of isolated uricase in which at least about 90% is present in a tetrameric form. Indeed, Lee does not even expressly disclose purifying a tetrameric form of uricase, disclosing instead only the purification of uricase monomers by SDS-PAGE. Thus, in disclosing "purification to homogeneity" of porcine and murine uricases, Lee is preparing uricase *monomers* and *not* uricase preparations in which at least about 90% of the uricase is tetrameric, as is presently claimed. That is, contrary to the Examiner's contentions, "homogeneity" in Lee does *not* mean "greater than about 90% tetrameric" or 100% tetrameric -- instead, one of ordinary skill would readily understand that "homogeneity" as used in Lee only means that the uricase has been rendered monomeric and has been purified away from non-uricase contaminants. Thus, this statement in Lee relating to homogeneity says nothing about the form, tetrameric or non-tetrameric, in

[3] Appellants would also like to note that none of the gel electrophoresis results in Lee show the migration of any proteins, only nucleic acids. *See* Figure 1C and Figure 3A-B of Lee. This reference only refers to the methods of Conley for the purification of the uricase by SDS-PAGE, and contains no mention of native gel electrophoresis of any proteins.

which the uricase of Lee exists prior to SDS-PAGE analysis -- indeed, the statement in Lee to the form of the uricase relates *after* SDS-PAGE analysis, *i.e.*, 100% monomeric. As one of ordinary skill would know, a homogenous preparation of isolated monomeric uricase -- which is the only isolated uricase expressly disclosed in Lee -- is not the same as an isolated tetrameric uricase which is recited by the present claims. Thus, as one of ordinary skill would readily appreciate, Lee does not expressly disclose the production of mammalian uricases having the characteristics recited in the present claims.

II. Lee Does Not Expressly Or Inherently Disclose Each And Every Element Of Claims 50-53

As indicated above, the Examiner has pointed to no express disclosure in Lee that would support the Examiner's incorrect and overly broad statement that the "homogeneous preparations of porcine or murine tetrameric uricase disclosed by Lee *et al.* is no different than the claimed uricase." *See* Examiner's Answer at page 6. Furthermore, the present specification clearly shows that by preparing uricases according to the methods of Lee, one of ordinary skill at best would succeed in preparing uricases that contain *less* than about 90% tetrameric uricase. Indeed, for the reasons discussed above, the methods of Lee would result in a uricase preparation in which most, if not all, of the uricase was in a *monomeric*, not tetrameric, form. Thus, as indicated in the Appellants' Brief on Appeal, any reliance by the Examiner upon inherent anticipation by Lee is factually and legally unfounded.

Accordingly, Lee does not expressly or inherently disclose the presently claimed invention. Hence, under *Kalman*, this reference cannot support a rejection under 35

U.S.C. § 102(b). The rejection of claims 50-53 under 35 U.S.C. § 102(b) over Lee therefore should be reversed by the Board.

III. Conclusion

In light of the foregoing remarks, as well as those set forth in Appellants' Brief on Appeal filed April 20, 2006, Appellants respectfully submit that the final rejection of claims 50-53 under 35 U.S.C. § 102(b) is improper and should be reversed.

Respectfully submitted,

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